Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. Cochrane Database of Systematic Reviews 2007, Issue 2, Art No CD006044.

Design: Systematic Review of randomized trials

PICOS:

- Patients: adults with either acute pain or a variety of neuropathic pain conditions, including diabetic neuropathy, HIV neuropathy, postherpetic neuralgia (PHN), phantom limb pain, trigeminal neuralgia, Guillain Barre, and spinal cord injury
- Intervention: lamotrigine in any dose by any route of administration and any dose to achieve analgesia
- Comparison: placebo
- Outcomes: pain relief of 50% or greater, patient reported global impression of clinical change, pain on movement, light touch or at rest, and adverse effects
- Study types: Randomized clinical trials published in journals, exclusive of experimental pain or pain produced by other drugs

Search strategy and selection:

- Databases searched were MEDLINE and EMBASE through August 2006, and the Cochrane Library through 2006
- All studies were read by both authors and agreement was reached by discussion
- Quality was assessed by Jadad scale, which has 2 points for randomization, 2 points for blinding, and 1 point for follow-up/accounting for attrition
- 7 studies with 502 participants were included initially, but 1 study of acute pain was excluded because all patients were treated with buprenorphine, a potent analgesic

Results:

- 6 studies of chronic pain were included, and 6 conditions were studied: central post-stroke pain, diabetic neuropathy, HIV neuropathy, intractable neuropathic pain, spinal cord injury pain, and trigeminal neuralgia
- For post-stroke pain, 30 participants took lamotrigine or placebo for 8 weeks in a crossover study; lamotrigine was superior to placebo when the outcome was a 2 point reduction in pain intensity (12/27 with lamotrigine and 3/27 for placebo)
- For diabetic neuropathy, lamotrigine produced a 50% pain reduction in 12/27 patients, compared to 5/26 for placebo; this was not statistically significant
- For HIV neuropathy, one study claimed effectiveness for lamotrigine, but 50% of the patients dropped out, and this result was not considered interpretable; a second HIV study by the same author reported that patients taking anti-retroviral therapy had pain relief in 33/62 patients on lamotrigine and 9/33 patients on placebo; this was statistically significant (relative benefit 1.95), but there was not a significant effect in HIV patients not taking anti-retroviral therapy

- For intractable neuropathic pain, spinal cord injury pain, and trigeminal neuralgia, no statistically significant benefit was reported
- Adverse effects were not consistently reported; rash was reported in about 7% of patients for whom data was available

Authors' conclusions:

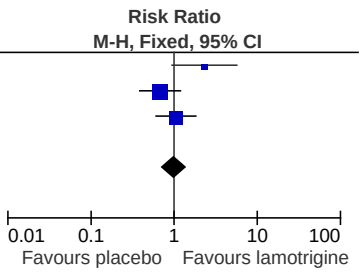
- Lamotrigine may have some benefit in post-stroke pain and in HIV neuropathic pain when patients are taking anti-retroviral therapy, but the small number of studies and participants is insufficient to support any robust conclusions
- Lamotrigine dose can be difficult to titrate, and its potential adverse effects include Stevens Johnson Syndrome
- Lamotrigine therefore is not likely to be of benefit in the treatment of neuropathic pain
- Other drugs are reasonably safe and effective; further research on lamotrigine is probably not warranted, due to the potential for harmful skin rash

Comments:

- Lamotrigine has a black box warning not only for Stevens Johnson syndrome but also for toxic epidermal necrolysis
- The comparison (placebo) was not stated in the methods section, but must be inferred from the comparisons made in the selected studies
- Publication bias is not discussed, but with only one article per condition under discussion, is not an issue in this setting
- Vinik 2007 compared lamotrigine 400 mg to placebo in two separate randomized studies of diabetic neuropathy published in one article; they can be combined with the data for Eisenberg 2001 to yield an estimate of no effect of lamotrigine in the following forest plot:

	Lamotrigine		Placebo			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Eisenberg 2001	12	27	5	26	10.8%	2.31 [0.95, 5.65]
Vinik 2007 b	16	87	23	85	49.1%	0.68 [0.39, 1.19]
Vinik 2007 a	20	84	19	84	40.1%	1.05 [0.61, 1.82]
Total (95% CI)		**198**		**195**	**100.0%**	**1.00 [0.71, 1.43]**
Total events	48		47			

Heterogeneity: Chi² = 5.21, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.03 (P = 0.98)



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- The authors' concerns about safety are appropriate in the context of a condition which has more effective and less hazardous treatments; one participant in Vinik 2007 required hospitalization for a lamotrigine related skin rash

Assessment: Adequate for good evidence that lamotrigine is not likely to be effective for the treatment of neuropathic pain, and that the potential harms are greater than the likely benefits